View metadata, citation and similar papers at core.ac.uk
brought to you by CORE
provided by Elsevier - Publisher Connector

REFERENCES

1. United States Renal Data System. 2011 *Annual Data Report: Atlas of Chronic Kidney Disease and End-Stage Renal Disease in the United States*. National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD, USA, 2011.
2. Bleyer AJ, Russell GB, Satko SG. Sudden and cardiac death rates in hemodialysis patients. *Kidney Int* 1999; **55**: 1553–1559.
3. Foley RN, Gilbertson DT, Murray T *et al.* Long interdialytic interval and mortality among patients receiving hemodialysis. *N Engl J Med* 2011; **365**: 1099–1107.
4. Zhang H, Schaubel DE, Kalbfleisch JD *et al.* Dialysis outcomes and analysis of practice patterns suggests the dialysis schedule affects day-of-week mortality. *Kidney Int* 2012; **81**: 1108–1115.

see original article on page 1116

Calcium balance in chronic kidney disease: walking the tightrope

Pieter Evenepoel[1], Liesbeth Viaene[1] and Bjorn Meijers[1]

Calcium supplements for prevention and treatment of mineral and bone disorders in chronic kidney disease (CKD) have been alternately praised and damned. Clinical evidence in favor of either attitude has been lacking. The calcium balance study by Spiegel and Brady in patients with late stage 3 and stage 4 CKD suggests that CKD subjects ingesting 2000 mg of elemental calcium per day are in marked positive balance. Methodological limitations such as unproven steady state warrant caution and confirmatory studies.

Kidney International (2012) **81,** 1057–1059. doi:10.1038/ki.2012.33

Calcium is an essential nutrient that plays a vital role in neuromuscular function, many enzyme-mediated processes, and blood clotting and provides skeletal rigidity by virtue of its phosphate salts. Its non-structural roles require the strict maintenance of ionized calcium concentration in tissue fluids, if necessary, at the expense of the skeleton. Calcium deficiency has been known for many years to jeopardize the skeleton in the long term. Recently, concerns have also grown that calcium supply in excess of the requirements may increase cardiovascular risk.[1] Avoiding calcium deficiency and overload, thus, is of utmost importance.

In normal adults, the rate of calcium absorption from the gastrointestinal tract matches the rate of losses from the body through the bowel, kidneys, skin, hair, and nails; that is, calcium balance is neutral (Figure 1). Age, bone disease, hormonal status, and exercise have all been shown to affect calcium balance.[2] An impaired gastrointestinal absorption, related to low 1,25-dihydroxyvitamin D_3 levels, and a decreased renal excretory capacity may render chronic kidney disease (CKD) patients at risk for either a negative or a positive calcium balance. However, studies investigating calcium balance in CKD are scant, probably because balance studies are labor-intensive and demanding. The new study by Spiegel and Brady[3] (this issue), therefore, is highly welcomed. These investigators performed balance studies in six patients with late stage 3 and stage 4 CKD and six control subjects consuming an 800- and a 2000-mg elemental calcium diet. Classical balance studies provide data for apparent absorption (intake minus fecal) and net retention (intake minus fecal minus urinary) and the corresponding coefficients. The main finding of the study is that CKD patients and healthy controls are in markedly positive calcium balance when ingesting 2000 mg elemental calcium, with calcium balance being significantly greater in CKD patients than in controls (759 versus 464 mg/d, mean). When ingesting an 800-mg calcium diet, conversely, both CKD patients and controls were in neutral to slightly negative calcium balance. On the basis of these observations the authors conclude that total elemental calcium intake should be within 800–1200 mg/d to prevent calcium deficiency and calcium loading, respectively. This implies that calcium supplements and calcium-containing phosphate binders are virtually completely to be avoided in CKD, even in patients not yet on dialysis. Is the evidence strong enough to support such a far-reaching conclusion? Several questions need to be raised and warrant caution.

A first question to be asked is whether or not the study participants were in steady state during calcium loading. It is well accepted that balances can be assessed only when patients are in steady state, that is, in the absence of major fluctuations in the homeostatic processes. Balance studies thus require sufficient equilibration time. A key question is what is sufficient time. Although there is no strong guidance from the literature, the 7-day equilibration period in the study by Spiegel and Brady[3] is rather short and might have been too short. The mean duration of balances in 210 studies from eight publications used in a recent report from the Food and Agriculture Association of the United Nations and the World Health Organization was 90 days.[4] Uncertainty as to whether a steady state is reached during calcium loading should especially caution against long-term extrapolation. Extrapolating from current data, a CKD patient treated with 4 g of calcium carbonate (1600 mg elemental calcium) would accrue approximately 2.8 kg elemental calcium over a 10-year time span. This amount of elemental calcium corresponds to about 6.8 kg of hydroxyapatite (1 mol $Ca_{10}(PO_4)_6(OH)_2 = 1004$ g; 1 mol Ca = 40 g), that is, roughly half the weight of the skeleton of a 68-kg person, which is hard to believe. These kinds of calculations, although tricky, at least raise doubts. Nonetheless, preliminary data from a

[1]*Division of Nephrology, Department of Medicine, University Hospital Leuven, Leuven, Belgium*
Correspondence: *Pieter Evenepoel, Dienst Nefrologie, Universitair Ziekenhuis Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.*
E-mail: Pieter.Evenepoel@uz.kuleuven.ac.be

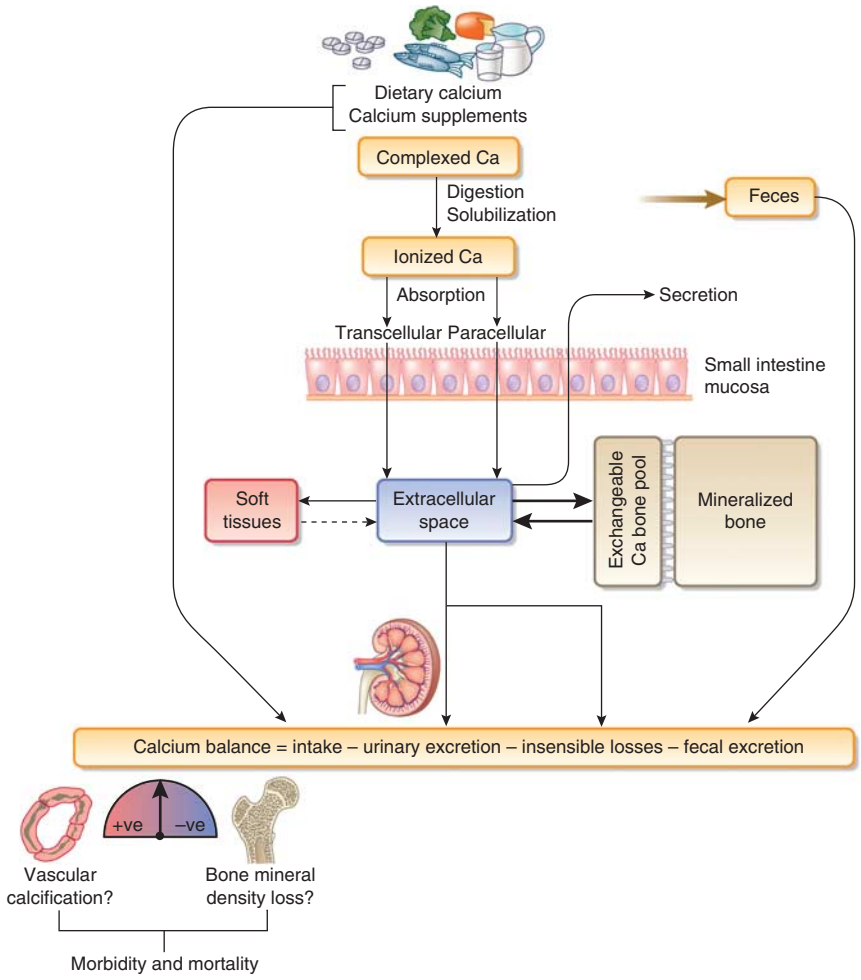

Figure 1 | Calcium balance: components and consequences.

recent 3–week balance study in CKD patients ($n = 3$) by Hill *et al.*, presented at the last American Society of Nephrology meeting (Kidney Week, Philadelphia, 2011, TH-OR015), corroborate the findings of Spiegel and Brady.[3] Patients ingesting 500 mg of elemental calcium three times a day with meals showed a markedly positive calcium balance (+404 mg/d), despite stable parathyroid hormone levels. It should be emphasized that this study, besides low patient number, is equally hampered by unproven steady state, despite the longer equilibration period. In future studies, steady state should ideally be confirmed by repeated measurements at intervals of sufficient duration (for example, 2 weeks) showing equal apparent absorption and net retention coefficients.

A second question relates to the validity of the balance data obtained during calcium loading. The validity of the results largely depends on how accurately the intake and output parameters are estimated. In the study by Spiegel and Brady,[3] feces and urine were collected for only a short time period. In addition, because of problems with the transit marker, the 24-h calcium losses in stool were calculated rather than directly determined. These calculations assumed a neutral phosphorus balance, which again cannot be proven. Calcium is a well-known phosphate binder, and phosphorus balance may be hypothesized to be at least transiently (more) negative during calcium loading. Consequently, the 'calculated' calcium balance overestimates the 'true' amounts retained during calcium loading. Skepticism on the validity of the data is fueled by two other observations made in the margin of the study. First, the authors report that the estimated percentage of ingested dietary calcium absorbed increased from 5 to 47% (mean) in CKD subjects and from 16 to 41% in controls on the 800- and 2000-mg calcium diets, respectively. This increase of the net fractional absorption during calcium loading is unexpected and opposite to what has been observed by others.[4] Second, parathyroid hormone levels significantly decreased during calcium loading, but the absolute decline was marginal and much less than one would expect if the calcium balance was truly positive by 759 mg/d.

As dietary calcium and phosphorus intake averages 800 and 1600 mg/d, respectively, in CKD patients, the above-mentioned objections of unproven steady state do not apply at the time of the baseline examination. In agreement with previous studies,[4,5] CKD patients ingesting their usual diet were found to be in neutral or in slightly negative calcium balance, even when insensible losses, which have been estimated at 40–80 mg/d, are not accounted for. Acknowledging that vascular calcification is observed in about 70% of patients with stage 3–4 CKD[6] and that calcium is rarely prescribed to these patients (either as a supplement or as a phosphate binder), it may be concluded that exogenous calcium plays only a minor role in the pathogenesis of vascular calcification. Opposite to vascular calcification, bone mineral content decreases with the progression of CKD.[7] Although it needs to be emphasized that calcium deficiency and negative calcium balance must sooner or later lead to osteoporosis, this does not mean that all osteoporosis can be attributed to calcium deficiency. Nonetheless, it would probably be generally agreed that any form of osteoporosis must inevitably be aggravated by negative external calcium balance. Such negative balance—even for short periods—is prejudicial because it takes so much longer to rebuild bone than to destroy it. Bone that is lost, even during short periods of calcium deficiency, is only slowly replaced when adequate amounts of calcium become available. All together, these data indicate that intestinal calcium fluxes are only a small component of overall balance; what really matters is the movement in and out of the bone, where 99% of the body calcium is stored.

Notably, the mean net fractional intestinal calcium absorption during habitual calcium intake was remarkably low in CKD patients (5% as opposed to 16% in controls). This low figure in CKD patients corresponds to data from previous balance studies.[5,8] Isotope tracer studies,[9,10] overall, yielded higher fractional intestinal calcium absorption rates (up to 25%) and less pronounced differences between healthy subjects and CKD patients. Tracer techniques, however, may overestimate real calcium absorption substantially, as they do not account for impaired calcium release from food (digestion and solubilization), which may be especially relevant in pathological conditions such as CKD.[11–13] Tracer techniques moreover require complex modeling that so far has not been validated in CKD.

In conclusion, Spiegel and Brady[3] should be heralded for providing highly needed calcium balance data in patients with CKD. Although it is currently clear that patients with CKD consuming their habitual diet are in neutral or even in slightly negative calcium balance, additional balance studies with adequate equilibration times and long collecting periods are required to teach us whether—and, if so, to what extent—calcium supplementation renders the calcium balance positive. Preferably, these balance studies should be combined with validated isotope techniques to define the destination of the excess calcium—the soft tissues or the bone. Given the enormous health implications and the current trend to initiate mineral metabolism therapy, including phosphate binders, in early-stage CKD, these studies are eagerly awaited. Undoubtedly, these studies will help us to walk the tightrope of health.

DISCLOSURE

The authors declared no competing interests.

REFERENCES

1. Elder GJ. Calcium supplementation: lessons from the general population for chronic kidney disease and back. *Curr Opin Nephrol Hypertens* 2011; **20**: 369–375.
2. Moe SM. Confusion on the complexity of calcium balance. *Semin Dial* 2010; **23**: 492–497.
3. Spiegel DM, Brady K. Calcium balance in normal individuals and in patients with chronic kidney disease on low- and high-calcium diets. *Kidney Int* 2012; **81**: 1116–1122.
4. Food and Agriculture Association of the United Nations and World Health Organization. *Human Vitamin and Mineral Requirements: Report of a Joint FAO/WHO Expert Consultation* 2012 Bangkok, Thailand. http://www.fao.org/docrep/004/Y2809E/y2809e0h.htm(2001, accessed 12 September 2012).
5. Clarkson EM, McDonald SJ, De Wardener HE. The effect of a high intake of calcium carbonate in normal subjects and patients with chronic renal failure. *Clin Sci* 1966; **30**: 425–438.
6. Budoff MJ, Rader DJ, Reilly MP *et al.* Relationship of estimated GFR and coronary artery calcification in the CRIC (Chronic Renal Insufficiency Cohort) Study. *Am J Kidney Dis* 2011; **58**: 519–526.
7. Klawansky S, Komaroff E, Cavanaugh Jr PF *et al.* Relationship between age, renal function and bone mineral density in the US population. *Osteoporos Int* 2003; **14**: 570–576.
8. Wilz DR, Gray RW, Dominguez JH *et al.* Plasma 1,25-(OH)2-vitamin D concentrations and net intestinal calcium, phosphate, and magnesium absorption in humans. *Am J Clin Nutr* 1979; **32**: 2052–2060.
9. Coburn JW, Koppel MH, Brickman AS *et al.* Study of intestinal absorption of calcium in patients with renal failure. *Kidney Int* 1973; **3**: 264–272.
10. Malluche HH, Werner E, Ritz E. Intestinal absorption of calcium and whole-body calcium retention in incipient and advanced renal failure. *Miner Electrolyte Metab* 1978; **1**: 263–270.
11. Bronner F. Nutrient bioavailability, with special reference to calcium. *J Nutr* 1993; **123**: 797–802.
12. Gueguen L, Pointillart A. The bioavailability of dietary calcium. *J Am Coll Nutr* 2000; **19**: 119S–136S.
13. Sheikh MS, Schiller LR, Fordtran JS. *In vivo* intestinal absorption of calcium in humans. *Miner Electrolyte Metab* 1990; **16**: 130–146.